PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	Docket No: Q65721
Praveen SHARMA, *et al.*	Group Art Unit: 1634
U.S. Patent Appln. No.: 10/727,576	Filed: December 5, 2003
Confirmation No.: 8084	Examiner: Juliet Caroline SWITZER

For: METHOD OF PREPARING A STANDARD DIAGNOSTIC GENE TRANSCRIPT PATTERN

PRE-APPEAL BRIEF REQUEST FOR REVIEW

MAIL STOP AF-PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the Pre-Appeal Brief Conference Pilot Program, and further to the Examiner's Final Office Action dated January 12, 2010, Applicants file this Pre-Appeal Brief Request for Review. This Request is also accompanied by the filing of a Notice of Appeal.

Applicants turn now to the two rejections for which review is requested.

1. Claims 18 and 20-25 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 6,190,857 to Ralph *et al.* in view of Lukas *et al.* (*Journal of Investigative Medicine*, 1997, 45(1): 132A).

2. Claims 19, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Ralph in view of Lukas as applied to claims 18 and 20-25, and further in view of Wadhwa *et al.* (*Molecular Biotechnology*, 6: 213-217).

As recognized by the Examiner, Ralph does not teach: (1) a method in which the organ defined cancer is very early stage breast cancer, (2) a method in which at least ten differently expressed markers are isolated, or (3) a method in which between 50 and 100 or between 10 and 500 mRNA or cDNA species are selected. See page 4 of Office Action mailed February 8,

2008. However, such deficiency is allegedly cured by Lukas, who teaches differential display analysis to identify genes that are differentially expressed in breast ductal carcinoma in situ (DCIS) relative to invasive breast carcinoma, and identifies 119 mRNA species which were differentially expressed in DCIS (a stage 0 breast cancer or "very early stage breast cancer"). Further, the Examiner recognizes that neither Ralph nor Lukas disclose a method in which identified isolated nucleic acid markers are prepared on a solid support. Id at page 6. However, such deficiency is allegedly cured by Wadhwa, who teaches a reverse Northern assay of DNA fragments isolated from differential display. On this basis, the Examiner proffers that the claimed invention would have been obvious because Ralph allows for detection and diagnosis of disease states that affect the peripheral blood leukocytes, by detection of markers produced by circulating leukocytes and not diseased cells, so that there is no requirement for direct interaction between cancer cells, their debris, or cellular components[1]. At pages 3 and 5 of the Office Action mailed January 12, 2010, the Examiner further contends that the arguments and Declarations of Dr. Mackay of record are not commensurate in scope with "most" of the claims which are directed to methods of screening the blood to identify differentially expressed transcripts that are markers for breast cancer, and not towards diagnosis of early stage breast cancer.[2]

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[1] According to the Examiner, detection may be feasible at very early stages of disease progression when there are few or no circulating cells present in the peripheral blood. Campbell (Biology, 4th Edition, 1996, page 833), is relied upon for the contention that it was known that white blood cells would come into contact with tumor cells via the interstitial fluid and the lymphatic system even if no blood vessels invaded the tumor. However, as Applicants noted on the record, mere contact between a blood cell and a tumor cell is not enough to allow detection by Ralph. Paragraphs 19-21 of the Second Declaration by Dr. Mackay, points out that pivotal to the success of the method by Ralph is the requirement for the cancer cell to have reached metastatic potential and thus, to display a metastatic phenotype. It is this metastatic phenotype which is detected or detectable by Ralph. Thus, even if blood cells did come into contact with very early stage breast cancer cells, no response of the kind observed by Ralph would have been expected, as those cells would not have reached metastatic potential.

[2] The arguments and evidence of record are commensurate in scope to the claimed invention because the present application provides a method of identifying transcripts or probes from a breast cancer sample that serve as a set of markers for diagnosis of very early stage breast cancer, as well as a method of preparing a transcript pattern standard for diagnosis of very early stage breast cancer using the transcripts or probes identified. See pages 3-4 and Examples of the original specification. The differentially expressed transcripts or probes identified are bound to a solid support and then hybridized to mRNA so that the amount of nucleic acid material that binds to the transcripts or probes is assessed and forms a transcript pattern standard of that disease

…(footnote continued)

For at least the following reasons, the Examiner has failed to establish a *prima facie* case. Further, any alleged *prima facie* case of obviousness is overcome because the present invention allows for the unexpected and surprising detection of non-metastatic or pre-metastatic cancers so that there would not have been a reasonable expectation of success of detecting such cancers based upon the method of Ralph.

First, in view of the deficiencies recognized above for Ralph and Lukas by the Examiner, and previously set forth on the record[3], neither Ralph nor Lukas[4], separately or in combination, teach or suggest all the presently claimed limitations. M.P.E.P. § 2143. Wadhwa does not cure the deficiencies of Ralph or Lukas, and does nothing further to render the claimed invention obvious, because Wadhwa is merely relied upon for teaching a technical assay, i.e., reverse Northern assay of DNA fragments isolated from differential display.

Second, Applicants have pointed out on the record, that "[e]vidence showing there is no reasonable expectation of success may support a conclusion of nonobviousness." M.P.E.P. 2143.02. See pages 5-7 of Response filed December 1, 2009. In this respect, the claimed invention allows for unexpected and surprising detection of non-metastatic or pre-metastatic cancers.

Ralph as a whole does not teach or suggest detection of non-metastatic or pre-metastatic

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or condition to be used for diagnosis. See pages 3-4 and Examples of the specification; see Declaration of Dr. Sharma and pages 14-16 of Amendment filed September 21, 2007; see pages 3-7 of Response filed October 29, 2007.

[3] See pages 4-6 of Response filed December 1, 2009, and pages 9-10 of Amendment filed March 27, 2009.

[4] Although Lukas teaches markers or differentially expressed genes for very early stage breast cancer, Lukas is deficient because Lukas at most teaches that tumor cells exhibit altered expression, and is entirely silent as to whether blood cells in a patient with breast cancer would have modified expression, or that such modified expression has diagnostic value. See footnote 3 at page 5 of Response filed December 1, 2009.

very early stage breast cancer[5] [6]. Rather, Ralph only teaches that markers may be detected for metastatic breast and prostate cancer.[7] As discussed in Dr Mackay's First Declaration filed March 27, 2009 (see paragraph 4) and Second Declaration filed December 1, 2009 (see paragraphs 7-14), one of ordinary skill in the art would have appreciated and taken the disclosure in Ralph[8] in context with the rest of the teachings, which is principally concerned with analysis of cancers that have reached metastatic potential or are metastatic, by showing that the peripheral blood of patients with metastatic disease exhibit markers which can be used to diagnose that disease. In this respect, these cells would reflect an altered phenotype and would have begun to release cells, debris or cellular components into the blood system allowing for the interaction of blood cells with the cells, debris or cellular components. In contrast, very early stage breast cancer which is non-metastatic or pre-metastatic does not release such cells, debris or cellular components into the blood system. See paragraphs 7-8 of First Declaration by Dr. Mackay filed March 27, 2009 and paragraph 15 of Second Declaration by Dr. Mackay filed December 1, 2009. Further, there is no teaching or suggestion by Ralph to obtain probes from non-metastatic or pre-metastatic breast cancer patients, or to prepare a gene transcript pattern for the diagnosis of cancers using such probes, as claimed. Rather, Ralph teaches generating probes from blood samples of patients with metastatic breast or prostate cancer

[5] As noted at pages 4-5 of Amendment filed December 1, 2009, there are fundamental differences between metastatic and non-metastatic or pre-metastatic cancers so that metastatic breast cancer cannot be equated to non-metastatic, very early stage breast cancer.

[6] See First Declaration by Dr. Mackay; pages 4-5 of Amendment and paragraphs 6-15 of Second Declaration by Dr. Mackay filed December 1, 2009.

[7] See all Examples of Ralph and Ralph at column 5, lines 55-57 (stating "[t]he instant disclosure demonstrates the success of this approach for the detection of metastatic prostate and/or metastatic breast cancer [emphasis added]."), column 6, lines 18-20 (stating "[a] number of markers for metastatic cancer of prostate or breast are described in the instant disclosure [emphasis added]."), column 6, lines 64 to 65 ("provides a simple and effective diagnostic test for the presence of cancer metastases [emphasis added]."), and column 7, lines 10-12 (stating "[t]he present disclosure represents a substantial and unexpected advance over previous knowledge in this field. It provides a sensitive means for detecting metastatic cancer…differentiating between BPH, localized and advanced forms of prostate cancer [emphasis added].").

[8] For example, at pages 3-4 of Office Action mailed January 12, 2010, the Examiner cites to column 5, lines 2-14 and column 14, line 55.

(see paragraph 15 Dr. Mackay's second Declaration filed December 1, 2009). Accordingly, one of ordinary skill in the art would only have extrapolated the teachings of Ralph to other cancers that are at a similar stage, i.e., cancers which have reached a metastatic phenotype and hence have detectable markers of that metastatic phenotype. This does not include very early stage breast cancer (see paragraphs 11 and 16 of Dr. Mackay's Second Declaration). Early stage disease as referred to by Ralph would be interpreted in the context of cancer as cancer which has begun to metastasize (see paragraph 12 of Dr. Mackay's Second Declaration). Extrapolation of the teachings of Ralph to the detection of cancers which have not reached a metastatic phenotype, e.g., very early stage breast cancer, as claimed, constitutes impermissible hindsight. M.P.E.P. § 2145.

Thus, because neither Ralph, Lukas, nor Wadhwa, separately or combined, teach or suggest that very early stage breast cancer may be detected or diagnosed using non-metastatic or pre-metastatic cancer cells, there would have been no reason or motivation for one of ordinary skill in the art to try to extend the teachings of Ralph to detect non-metastatic or pre-metastatic cancers because the teachings of Ralph may only be extrapolated to identifying early metastatic changes. Accordingly, one of ordinary skill in the art would not have had a reasonable expectation that the combination would successfully detect and diagnose very early stage breast cancer, as unexpectedly and surprisingly provided by the claimed invention, even in light of Lukas and/or Wadhwa. Further, even assuming *arguendo* these references are combined, one of ordinary skill in the art would not arrive at the presently claimed invention for the reasons discussed above and on record.

Withdrawal of the rejection is respectfully requested.

Respectfully submitted,

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Date: July 12, 2010